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ORIGINAL ARTICLE

Presence of interferon-λ 4, male gender, absent/mild steatosis and low viral load augment antibody levels to hepatitis C virus

Jesper Waldenström[a,b], Kristoffer Hellstrand[a,c], Johan Westin[a,b], Staffan Nilsson[d,e], Peer Christensen[f,g], Martti Färkkilä[h], Kristine Mørch[i], Nina Langeland[i], Gunnar Norkrans[a,b] and Martin Lagging[a,c]

[a]Department of Infectious Diseases/Virology, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [b]Department of Infectious Diseases, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden; [c]Department of Clinical Microbiology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden; [d]Department of Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden; [e]Department of Pathology and Genetics, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden; [f]Department of Infectious Diseases, Odense University Hospital, Odense, Denmark; [g]Institute of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark; [h]Department of Gastroenterology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [i]Department of Clinical Science, University of Bergen, Bergen, Norway

ABSTRACT

Objectives: Despite recombinant interferon-λ 4 (IFN-λ4) demonstrating anti-viral activity *in vitro* and the ancestral functional gene (*IFNL4*) being conserved in all other primates, there has been speculation that IFN-λ4 may be detrimental in humans. In light of recent rekindled interest in humoral immunity, this study aimed at evaluating the impact of baseline characteristics, including *IFNL4*, on antibody levels to hepatitis C virus (HCV).

Materials and methods: Pretreatment sera from 279 well-characterized North European Caucasians with chronic HCV genotype 2 or 3 infection having undergone liver biopsy were analyzed regarding *IFNL4* (rs12979860) and anti-HCV antibody levels using a commercially available assay.

Results: Patients producing IFN-λ4 had higher signal to cut-off (S/CO) anti-HCV antibody ratios as compared with those lacking IFN-λ4 ($IFNL4_{rs12979860}$ CT/TT versus CC, $p<.0001$, Mann–Whitney *U*-test). Additionally, in univariate analyses S/CO was significantly higher in men than women ($p<.001$), as well as in patients with absent/mild interface hepatitis (Ishak grade 0–2 versus 3–4, $p=.009$), and absent/mild steatosis (grade 0–1 versus 2–3, $p=.0005$). Also, an inverse correlation with HCV RNA level ($r_s=-0.14$, $p=.02$) was noted. In multivariate analysis IFN-λ4, gender, steatosis and viral load remained independently associated.

Conclusions: To our knowledge, this is the first report that demonstrates that the ability to produce IFN-λ4, in addition to male gender, absent/mild steatosis, and lower viral load, augments antibody levels against HCV. This indicates that IFN-λ4 may be associated with T helper cell 2 (Th2) immune skewing, which might have clinical implications beyond HCV infection.

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Introduction

Homozygous carriage of the C allele in rs12979860 in the proximity of the interleukin 28B gene (*IL28B* also known as interferon-λ 3 (*IFNL3*)) on chromosome 19 substantially increases the likelihood of spontaneous clearance of acute hepatitis C virus (HCV) infection [1] as well as improved outcome following interferon-based HCV therapy [2,3]. Recently, however, this single-nucleotide polymorphism (SNP) was found to be located in intron 1 in a novel, previously overlooked gene encoding interferon-λ4 (*IFNL4*), and to be in strong linkage disequilibrium (LD) with an insertion/deletion polymorphism in *IFNL4* exon 1 (rs368234815). Humans are polymorphic for the dinucleotide TT/ΔG allele in rs368234815 [4], with the TT allele resulting in a frameshift which leads to pseudogenization of *IFNL4* and nullification of IFN-λ4 production. In contrast, the ancestral wild-type allele $\Delta G_{rs368234815}$, which is present in all non-human primates [5], allows for production of IFN-λ4.

IFN-λ4 is the most divergent member of the IFN-λ family and has only 29% amino acid identity with IFN-λ3, unlike the >80% homology observed between IFN-λ1, IFN-λ2 and IFN-λ3 [4]. Recombinant IFN-λ4 signals through the IFN-λ receptor 1 [6] to activate the JAK/STAT pathway, which subsequently induces expression of interferon-stimulated genes (ISGs). This in turn leads to high anti-viral activity, although the amino acid substitution K154 fixed throughout evolution

CONTACT Martin Lagging martin.lagging@medfak.gu.se Department of Infectious Diseases/Virology, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Guldhedsgatan 10B, Gothenburg SE-413 46, Sweden

in hominid lineages reduces the secretion and potency of IFN-λ4 in comparison to the ancestral E154 found in IFN-λ4 in chimpanzee and other mammals [7].

IFN-λ4 expression *in vitro* in human hepatic cells (HepG2 and primary human hepatocytes (PHHs)) results in significant intracellular retention of IFN-λ4, reduced proliferation, increased cell death, but also in strong activation of ISGs in surrounding cells [8]. Also, IFN-λ4 induction in Huh-7, HepG2 and PHHs cells leads to interferon-α unresponsiveness by upregulating levels of ISG15 and ubiquitin specific peptidase 18 (USP18) [9].

Aside from impacting on HCV infection, abrogation of IFN-λ4 is also associated with more severe steatosis (Kleiner grade 3), lobular inflammation (grade 2–3), and hepatic fibrosis (stage F3–F4) in nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) especially among nonobese individuals [10]. Similarly, inability to produce IFN-λ4 is associated with increased risk of some autoimmune disorders, e.g., lupus nephritis in systemic lupus erythematosus (SLE) [11] and pulmonary fibrosis in systemic sclerosis (aka scleroderma) [12], as well as with lower frequencies of regulatory T cells (T_{reg}) in colonic tissue biopsies [13].

Several studies have focused on IFN-λ4 and impaired adaptive and innate immunity [14,15], and unexpectedly there is scant *in vivo* evidence of potential benefits of having a functional *IFNL4* gene aside from lower risk of some autoimmune diseases, despite being highly conserved in other primates. In light of this as well as renewed interest in humoral immunity, this study aimed at evaluating the impact of *IFNL4* variants on anti-HCV antibody levels using a commercially available assay in a well-characterized cohort of North European Caucasian patients with chronic HCV genotype 2 or 3 infection having undergone liver biopsy.

Materials and methods

Study population

Three hundred eighty-two genotype 2 or 3 infected patients were enrolled in the NORDynamIC trial [16] and previously genotyped for $IFNL4_{rs12979860}$ [17]. Pretreatment sera from 279 of these well-characterized patients of North European Caucasian origin (baseline characteristics summarized in Table 1) could be retrieved and analyzed for anti-HCV antibody responses in this study.

Anti-HCV antibody detection

All samples were analyzed using the chemiluminescent microparticle immunoassay on the Alinity instrument (Abbott, Chicago, IL) in accordance with the manufacturer's instructions. The assay measures the amount of anti-HCV antibodies against the recombinant HCV proteins HCr43 expressed in *Escherichia coli* (prepared by Chiron Corporation, Emeryville, CA), containing amino acids 1–150 in core and 1192–1457 (33c) in NS3, and c100-3 expressed in *Saccharomyces cerevisiae* (prepared by Chiron Corporation, Emeryville, CA), containing amino acids 1569-1931 in NS3, NS4a and NS4b. The chemiluminescent reaction is measured as relative light units (RLUs) detected by the system optics, and there is a direct relationship between the amount of anti-HCV in the sample and RLUs. A signal-to-cutoff ratio (S/CO) is determined by comparing the chemiluminescent RLUs in the reaction to the cutoff RLUs determined from an active calibration, and S/CO $\geq$1.0 is considered reactive. All sera were stored at −80 °C until analyzed.

IFNL4 genotyping

Rs12979860 polymorphisms in chromosome 19 were determined in serum by allelic discrimination using Taq-Man SNP Assays (Life Technologies, Carlsbad, CA) using an in-house test as described previously [17].

HCV-RNA detection and genotyping

All HCV RNA samples were analyzed by Roche COBAS AmpliPrep/COBAS TaqMan HCV test as described by the manufacturer.

Table 1. Baseline characteristics of the 279 patients included in the study.

Feature	All patients $n = 279$
Epidemiological features	
Age (years), mean (SD)	42.8 (10.7)
Sex (male), *n* (%)	164 (58.8)
BMI (kg/m^2), mean (SD)	25.9 (4.2)
Characteristics of HCV infection	
HCV-RNA at baseline (log10 IU/mL), mean (SD)	6.0 (0.9)
HCV genotype (genotype 2/3/2 + 3), *n* (%)	83/194/2 (29.7/69.5/0.7)
Ishak fibrosis stage (0/1/2/3/4/5/6), *n*	7/32/73/65/37/15/25
Cirrhosis, *n* (%)	40 (14.3)
Ishak interface hepatitis grade (0/1/2/3/4), *n*	12/81/93/63/5
Ishak lobular inflammation grade (0/1/2/3/4), *n*	1/51/156/44/2
Ishak portal inflammation grade (0/1/2/3/4), *n*	10/114/107/23/0
Steatosis grade (0/1/2/3), *n*	85/102/45/22
Anti-HCV S/CO ratio, AU (SD)	13.0 (2.7)
Host genetics	
IFNL4 rs12979860 T allele carrier yes/no (%)	157/122 (56%)

HCV: hepatitis C virus; SD: standard deviation; SVR: sustained virologic response.

Liver biopsies

Liver biopsies were obtained from all patients within 12 months prior to study entry. The evaluation was performed in a blinded fashion according to the Ishak protocol [18]. Additionally steatosis was graded [19].

Statistical analyses

Mann–Whitney *U* test was used when comparing the amount of anti-HCV antibodies between groups. Logistic regression was applied after dichotomization of anti-HCV antibodies above or below study median. All parameters with a *p*-value above .1 in the univariate analysis was included in the multivariate analysis after checking for multicollinearity. Statistics was done in Prism (Version 9.0.1, GraphPad Software, La Jolla, CA) or SPSS (Version 27, IBM Corp, Armonk, NY) software. All reported *p* values are two-sided, and *p* values $<.05$ were considered significant.

Ethical considerations

Written informed consent was obtained from each participating patient, and ethics committees in each participating country approved the study. The study has been registered at the NIH trial registry (ClinicalTrials.gov Identifier: NCT00143000).

Results

IFNL4 and anti-HCV antibody level

A highly significant relationship between $IFNL4_{rs12979860}$ genotype and S/CO antibody level was observed (Figure 1(A)), with the lowest antibody levels (S/CO) observed in the absence of IFN-λ4 ($IFNL4_{rs12979860}$ CC genotype) as compared to one ($IFNL4_{rs12979860}$ CT) or 2 functional *IFNL4* genes ($IFNL4_{rs12979860}$ TT).

As $IFNL4_{rs12979860}$ genotype is known to associate with interferon gamma-induced protein 10 (IP-10 aka CXCL10) [20], the correlation between IP-10 and S/CO was also explored, and a non-significant trend was noted towards higher anti-HCV antibody levels when IP-10 concentrations were lower ($p = .06$).

As $IFNL4_{rs12979860}$ genotype is known to associate with sustained virologic response (SVR) following interferon and ribavirin combination therapy for HCV, the correlation between SVR and S/CO was evaluated but was not significant.

Gender and anti-HCV antibody level

A marked gender difference in antibody levels was noted, with significantly higher S/CO in men as compared to women ($p<.0001$; Figure 1(B)). For both gender the ability to produce IFN-λ4 entailed significantly higher antibody levels (Figure 1(C)).

Histopathology and anti-HCV antibody level

Significantly higher S/CO antibody levels were observed among patients with absent/mild interface hepatitis (Ishak grade 0–2 versus 3–4, $p = .009$; Figure 2A) and absent/mild steatosis (grade 0–1 versus 2–3, $p = .0005$; Figure 2B). As body mass index (BMI) and HCV genotype 3 infection are known to associate with steatosis [19], their associations with anti-HCV S/CO were evaluated but were not significant (Table 2). A non-significant trend was noted towards lower antibody levels in patients with significant fibrosis (Ishak stage 0–2 versus 3–6 median 13.9 versus 13.0 respectively, $p = .06$). Please note, however, that when using univariate logistic regression this association was significant ($p = .02$; Table 2).

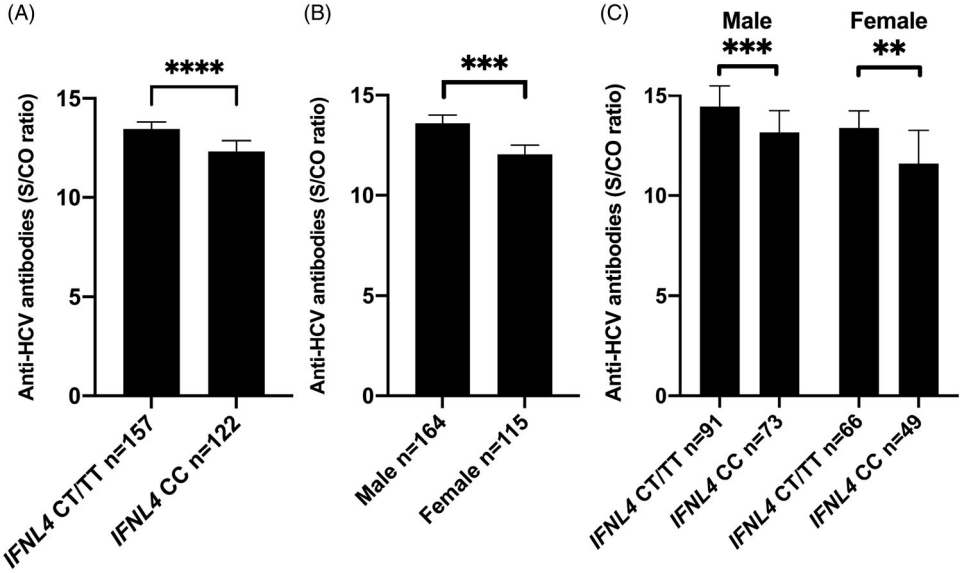

Figure 1. Signal-to-cutoff (S/CO) antibody ratio in relation to the absence of IFN-λ4 ($IFNL4_{rs12979860}$ CC) or presence of IFN-λ4 ($IFNL4_{rs12979860}$ CT/TT) (A), gender (B), and gender and IFN-λ4 (C). Median and interquartile range. Statistics using Mann–Whitney *U* test.

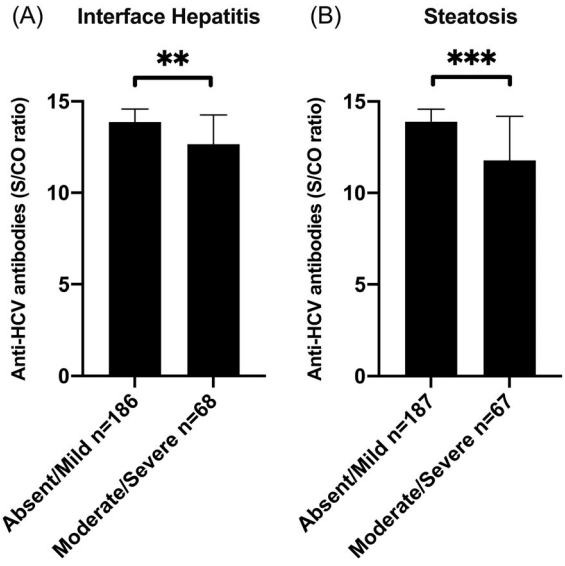

Figure 2. Signal-to-cutoff (S/CO) antibody ratio in anti-HCV antibody assay in relation to absent/mild or moderate/severe interface hepatitis (Ishak grade 0–2 versus 3–4) (A), and absent/mild or moderate/severe steatosis (grade 0–1 versus 2–3) (B). Median and interquartile range. Statistics using Mann-Whitney *U*-test.

Table 2. Associations of baseline characteristics with anti-HCV S/CO ratio.

	Univariate logistic regression			Logistic regression		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Epidemiological features						
Age (years)	0.97	0.95–0.99	**.01**	0.99	0.96–1.02	.56
Sex (female)	0.33	0.20–0.54	**<.001**	0.19	0.10–0.36	**<.001**
BMI (kg/m^2)	1.02	0.96–1.08	.6			
Characteristics of HCV infection						
HCV-RNA at baseline (log10 IU/mL)	0.65	0.49–0.87	**.003**	0.62	0.43–0.88	**.008**
HCV genotype (genotype 2/3)	0.96	0.57–1.6	.87			
Ishak fibrosis stage	0.82	0.79–0–97	**.02**	0.88	0.67–1.15	.35
Ishak inflammation grade (sum of score)	0.86	0.75–0.98	**.02**	0.96	0.78–1.18	.67
Steatosis grade	0.70	0.53–0.92	**.01**	0.70	0.51–0.96	**.03**
Host genetics						
IFNL4 rs12979860 CC carrier yes/no (%)	0.42	0.26–0.68	**<.001**	0.51	0.29–0.89	**.02**

Significant values are highlighted in bold.

HCV RNA concentration and anti-HCV antibody level

An inverse correlation with HCV RNA level ($r_s = -0.14$, $p = .02$) was noted. Although HCV RNA previously has been reported to be significantly higher in genotype 3 infected patients lacking IFN-λ4 (*IFNL4*$_{rs12979860}$ CC genotype) as compared those with a functional gene (*IFNL4*$_{rs12979860}$ CT/TT) enrolled in the NORDynamIC trial [17], no significant differences in anti-HCV S/CO between patients infected with genotypes 2 and 3 were observed (Table 2).

Multivariate analysis and anti-HCV antibody level

Parameters associated with an anti-HCV S/CO value above or below study median were evaluated using logistic regression. IFN-λ4 genotype, gender, steatosis and viral load remained independently associated with the anti-HCV S/CO value (Table 2).

Discussion

The main findings of this study were that ability to produce IFN-λ4, in addition to male gender, absent/mild steatosis, and lower viral load, augmented antibody responses against HCV, and that highest antibody ratios were observed in carriers with two functional genes (*IFNL4*$_{rs12979860}$ TT homozygotes) in both genders. To our knowledge, this is the first study to demonstrate that the ability to produce IFN-λ4 is associated with higher antibody levels against HCV.

Despite recombinant IFN-λ4 being highly antiviral *in vitro* [7], and signaling through the IFN-λ receptor 1 to activate the JAK/STAT pathway and subsequently inducing expression of ISGs, the ability to produce IFN-λ4 *in vivo* is predictive of inferior likelihood of spontaneous resolution of acute HCV infection [1] and unresponsiveness to interferon and ribavirin combination treatment [2,3]. Members of the IFN-λ family generally tend to favor a Th1 skewed immune response, i.e., greater activation of macrophages, cytotoxic T cells and NK cells as well as less stimulation of antibody producing B cells. However, data on IFN-λ4, which is the most divergent member of the interferon-λ family [4], are scarcer in this regard [21]. Interestingly, following immunization of 91 kidney, 64 lung, 24 liver and 17 heart transplant recipients on maintenance immunosuppression enrolled in a trial of intradermal versus intramuscular influenza vaccine, increased rates of

seroconversion (i.e., ≥4-fold rise in titer from pre-vaccination to at least one of the three vaccine antigens) were noted in individuals capable of producing IFN-λ4 (*IFNL4*$_{rs8099917}$ TG/GG) [22], although the ethnic and racial background of the study population was not reported. Similarly, carriage of the minor G allele in rs10853727 located within *IFNL4* has been associated with significantly higher antibody titers following measles vaccination in racially and ethnically diverse pediatric populations in two independent studies [23,24], although the impact of this particular SNP on expression or function of IFN-λ4 remains unclear. Together these previous studies support the observation noted in the present study that ability to produce of IFN-λ4 entails improved antibody responsiveness. However, the present study extends upon these findings as it excludes the potential confounding effect of ethnic and racial background, which are known to impact on many aspects of vaccine efficacy [25].

The finding in this study suggesting that presence of IFN-λ4 predisposes towards a Th2-skewed immune response is intriguing and may indicate a shift from B- to T-cell responsiveness in humans following evolutionary pressure. Interestingly, the frameshift mutation in *IFNL4* that rescinds IFN-λ4 production has been suggested to have appeared in homo sapiens just prior to the out-of-Africa migration, and thereafter enriched by positive selection [26]. It is, thus, tempting to hypothesize that in smaller, isolated hunter–gatherer societies where exposure to epidemic pathogens is unlikely, Th2 responses may have greater importance, for example, stronger maternal antibody responses against enteric and endemic pathogenic microorganisms leading to reduce infant mortality. In contrast, after marked population growth occurred following the development of agriculture and domestication of animals in the Neolithic Revolution and subsequent urbanization, the introduction and spread of novel zoonic epidemic infectious agents was greatly facilitated, selecting for enhanced Th1 responsiveness by reducing or annulling the production of IFN-λ4.

The observation in the present study that antibody ratios were significantly higher in men than in women is in line with well-documented gender differences in immune responses observed in numerous vaccine trials [27], as well as following SARS-CoV-2 infection [28].

The impact of hepatic histopathology on antibody levels is noteworthy, and, to our knowledge, the highly significant association with steatosis has not previously been reported. In univariate analysis, interface hepatitis was also significant, but in multivariate analysis, steatosis grade was the only aspect of liver histopathology that remained independent associated with antibody levels, with more pronounced steatosis being linked with significantly lower antibody levels. This was somewhat surprising as neither body mass index (BMI) nor HCV genotype 3 infection, which both are known to associate with steatosis [19], were not significantly associated with anti-HCV antibody levels. Interestingly, obesity is reported to be associated with a heightened state of immune activation as exemplified by elevated antibody titers to heat-shock protein-27 [29], which additionally controverts the notion that higher BMI was driving the association between steatosis and antibody levels observed in this study.

The inverse correlation between anti-HCV antibody ratios and HCV RNA level was expected as baseline HCV RNA levels are reportedly elevated in the absence of IFN-λ4 (*IFNL4*$_{rs12979860}$ CC) [17]. However, in the multivariate analysis, both viral load and *IFNL4* genotype were independently associated with anti-HCV antibody levels.

In conclusion, the present study demonstrated that *IFNL4* genetic variants resulting in ability to produce IFN-λ4 are linked with elevated anti-HCV antibody levels. This finding implies that IFN-λ4 may impact on host antibody responses and warrants further investigation as this likely has clinical implications beyond HCV, e.g., levels of antibody against other viruses.

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Disclosure statement

The authors report no conflict of interest.

Author contributions

Je.Wa.: concept and design, experiments and procedures, and writing of article; K.H.: experiments and procedures, and writing of article; Jo.We.: concept and design, and writing of article; S.N.: experiments and procedures, and writing of article; P.C.: concept and design, and writing of article; M.F.: concept and design, and writing of article; K.M.: concept and design, and writing of article; N.L.: concept and design, and writing of article; G.N.: concept and design, and writing of article; M.L.: concept and design, experiments and procedures, and writing of article.

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ORCID

Jesper Waldenström http://orcid.org/0000-0003-2234-0076
Kristoffer Hellstrand http://orcid.org/0000-0002-6617-5976
Martti Färkkilä http://orcid.org/0000-0002-0250-8559
Martin Lagging http://orcid.org/0000-0002-7995-3626

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